UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

001374

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: January 22, 1982

SUBJECT: Review of Data for Metolachlor, IDD-597
Acc. No. 345957-61 Tox. Chem. 188DD

FROM: Gary J. Burin, Toxicologist Gary J Burin 1/22/82
Toxicology Branch/HED (TS-769)

TO: Richard Mountfort (23)
Registration Division (TS-767)

TRHU: Orville E. Paynter, Chief
Toxicology Branch/HED (TS-769)

Registrant: Ciba-Geigy Corporation
Agricultural Division
P.O. Box 18300
Greensboro, North Carolina 27419

Review of Data

1) One-Year Interim Report on a Two-Year Oral Feeding Study of Metolachlor in Rats, conducted at Raltech Scientific Services and submitted by Ciba-Geigy on 9/30/81.

Albino CD rats are being fed either 0, 30, 300 or 3000 ppm of technical Metolachlor in the diet. Sixty animals per group were started on test and an additional 10 animals were included in the control and high dose groups for use as "recovery" animals after 52 weeks of testing.

Apparent compound related effects were only observed in the 3000 ppm group. Females were significantly reduced in mean body weight at that dose level and depressed weight gain had been observed for throughout most of the study (weeks 2, 5, 8, 13-52). SGOT and SGPT were significantly reduced in males after 12 months. Liver to body weight ratios of males sacrificed at 12 months were significantly increased. No gross or microscopic findings were observed that appear

to be treatment related. Five animals removed from exposure to test compound (at the 3000 ppm level) for a one month recovery period showed an increased weight gain compared to controls, suggesting that depressed weight gain resulting from metolachlor exposure is at least partially reversable for rats of this age. No compound related effects were observed for clinical observations, hematology, clinical chemistry (other than SGOT and SGPT), urinalysis or organ weights other than liver. No apparent compound related effects were observed at the 30 or 300 ppm dose levels.

Core Classification

Supplementary Data. A NOEL of 300 ppm is suggested at this point in the study. This study, combined with an earlier 90-day rat feeding study, satisfies the requirement for a subchronic feeding study in the rat per letter of February 18, 1981 from Registration Division to Ciba-Geigy.

2. Two-Generation Reproduction Study with Metolachlor Technical in Albino Rats, conducted at Raltech Scientific Services and submitted by Ciba-Geigy on 9/30/81.

Metolachlor Technical was fed in the diet at dose levels of 0, 30, 300 or 1000 ppm to Charles River CD strain albino rats. Fifteen male and 30 females were assigned to each treatment group and were 32 days old when they first received test compound. Animals were mated after either 14 weeks (F_0) or 17 weeks (F_1) on test. Mating only occurred once per generation.

The F_1 parental animals were randomly selected from the F_{1a} litter after weaning of F_{1a}. F_0 males were sacrificed after 135 days on test and F_0 females were sacrificed after 164 days on test. Gross examination was conducted on all F_0 males and on F_0 females which displayed "untoward developmental anomalies". After 157 to 167 days on test, F_1 males were sacrificed and after 197 to 208 days, F_1 females were sacrificed. Gross and histological examinations were performed on all F_1 parents. Five randomly selected male and 5 female F_{1a} progeny in each dose group were also examined histologically.

The total number of pups, number delivered viable or stillborn and number found cannibalized were recorded for each litter. Pup survival to days 1, 4, 7, 14 and 21 after birth were recorded. Litters greater than 10 pups were randomly reduced in size on day 4. Pup body weights were recorded on days 4, 7, 14 and 21. Litters were observed daily.

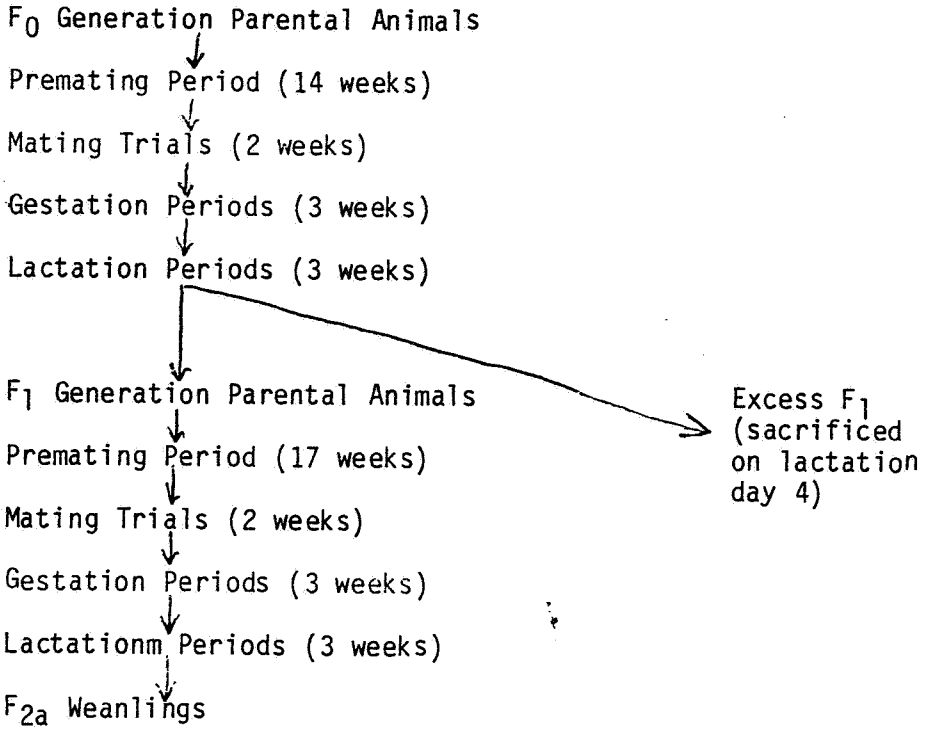
Food consumption was measured weekly for each parental animal of the F_0 and F_1 generations only during the premating periods. Diet analyses were conducted on 15 separate occasions.

Organ weights for adrenal, brain, heart, kidneys, liver, spleen, testes and thyroid were recorded for all F_1 parental animals surviving to final sacrifice. The following tissues were examined histologically:

Adrenal	Pituitary
Aorta	Prostate
Bone (with marrow)	Salivary gland
Brain (3 levels)	Sciatic nerve
Esophagus	Skeletal muscle
Eyes	Skin
Heart	Small intestine
Kidneys	Spinal cord
Large intestines	Spleen
Liver (2 lobes)	Stomach
Lung	Testes
Lymph nodes	Trachea
Mammary gland	Thymus
Ovaries	Thyroid (with parathyroid)
Pancreas	Urinary bladder
	Uteri

In addition, all tissues appearing abormal were examined microscopically.

The study design was essentially as follows:



Results

Time weighed average concentrations of metolachlor, based on periodic diet analyses, were 0, 32.0, 294 and 959 ppm for the 0, 30, 300 and 1000 ppm groups, respectively. No deaths occurred among the F_0 animals or among the F_1 males. Two F_1 females were found dead during the premating period, one F_1 female was found dead on gestation day 19 and one F_1 female was sacrificed in moribund condition on lactation day 1; these animals belonged to the 300, 1000, 300 and 0 ppm groups respectively. No compound related effect on parental body weight was apparent. Food consumption was not effected by treatment in the F_0 generation but was significantly reduced for the F_1 30 ppm females at week 16, 300 ppm females at weeks 6, 7 and 10 and the 1000 ppm females at weeks 1, 6, 7, 8, 10, 12, 13 and 15, as compared to controls.

Clinical observations of parental animals did not indicate effects which could be associated with treatment. The mating, gestation, lactation, female fertility and male fertility indices did not appear to be effected by treatment in either generation. Pup survival was also not effected by treatment.

Pup body weights of the 1000 ppm dose level group were significantly reduced for the F_{1a} litters on days 14 and 21 and on days 4, 7, 14 and 21 for the F_{2a} litters. Pup body weights of the 30 and 300 ppm dose groups did not appear to be effected in a compound-related manner.

The incidence of external anomalies observed in pups did not appear to be effected by treatment. Gross and histological examination of parents and progeny did not reveal any lesions which appeared to be related to treatment.

Liver to body weight ratios were significantly increased for both F_1 parental males and females at the 1000 ppm dose level. The thyroid to body weight ratio and the thyroid to brain weight ratio of 1000 ppm F_1 males were significantly increased. Other organ weight comparisons that were statistically significant compared to controls did not appear to be related to treatment. Body weights of the weanling 1000 ppm F_{1a} females and F_{2a} males were reduced, though not significantly, and body weights of F_{2a} weanling females were significantly reduced for the 1000 ppm dose level.

Core Classification

Core Guidelines. The NOEL for reproductive effects is 300 ppm based on reduced pup weights and reduced parental food consumption at 1000 ppm. Other effects that may be related to treatment were increased liver to body weight and thyroid to body weight ratios in the 1000 ppm F_1 parents.

TS-769:th:TOX/HEDGJBurin:1-22-82:card 2